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BIOTECHNOLOGY IN JAPAN: 1990 UPDATE

Summary

Barely a decade after its birth, Japan's biotechnology industry is showing signs of both youth and maturity. Since JEI last surveyed this topic (JEI Report No. 5A, February 7, 1986), a handful of products incorporating biotechnology has reached Japanese consumers, in some cases meeting with resounding success. The scope of biotechnology in Japan, however, is expanding so rapidly that the term bioindustry or life industry has been coined to include such nontraditional applications as bioactive intelligent materials. The biotech bandwagon is attracting an increasingly diverse group of Japanese companies with long-term commitments in mind. The Japanese government continues to encourage this trend with support for basic and long-term research and commercialization efforts. Being younger than the U.S. or European biotech industries, Japan's has not yet begun to seriously grapple with difficult issues such as bioethics, intellectual property issues or regulatory standards. Although most Japanese still consider their industry to be trailing American and European competitors, they are equally confident that Japan will play a major role in the global biotechnology industry.

Entering Adolescence?

It has taken three decades for scientists to transform a basic understanding of the structure of the gene (a sequence of deoxyribonucleic acid (DNA) that controls the expression of a trait in an organism) into products that affect everyday lives. Despite its tardy birth in 1980 (more than half a decade behind the United States and Europe), the Japanese biotech industry has not been far behind its American and European counterparts in the introduction

of biotech products. Although this is due in large part to active licensing of foreign technology by Japanese firms, homegrown products are also for sale.

Not surprisingly, medical testing and pharmaceutical markets have the greatest number of biotech products. Products isolated and analyzed via biotechnology but produced by traditional means have become almost commonplace as have goods produced with biotech from start to finish. A wide range of diagnostic kits using biotech reagents are available in both the medical and the agricultural fields. Several substances that occur naturally within the human body now are on sale for therapeutic use thanks to biotechnology, including human growth hormone, antitumor treatments and agents that either dissolve or encourage blood clotting. Industry observers report at least four dozen biotech drugs in the clinical testing pipeline that should come to market within five years.

Biotech's presence in the food and agriculture sectors also is growing. Pesticides composed of genetically altered or specially selected naturally occurring bacteria are gaining wider acceptance in the face of consumer concerns over traditional chemical agents. Japanese consumers also can purchase four wines made with biotechnologically developed yeast cultures and a vegetable that exists only because of cell fusion technology and in vitro cell growth techniques. A few food testing kits using the targeted properties of monoclonal antibodies are coming to market. Most analysts agree, however, that it will be five to 10 years before biotechnology has a significant impact on Japan's seed, fresh vegetable and processed food markets.

Biotech cosmetics and cleaners have given their makers an edge over rivals in intensely competitive domestic markets. While canny marketing plans certainly have contributed to the commercial success of these products, the fact that the goods live up to manufacturers' performance claims, according to consumer surveys, plays an equally important role. Shiseido Co., Ltd. and Kao Corp. are both contemplating overseas launches of their biotech products.

In addition to companies strengthening their traditional product lines through biotechnology, a second wave of companies has seized upon the know-how as a means to diversify. Yamasa Shoyu Co., Ltd. realized several years ago that demand for soy sauce would weaken as foreign foods increasingly became a part of Japanese life. At first focusing on other food flavorings based on amino acids (the building blocks of proteins), Yamasa then jumped into the biochemical reagent market using expertise gained with nucleic acids in flavorings. Yamasa currently supplies nucleic acids critical to producing some drugs, such as beta interferon and azidothymidine (AZT), as well as diagnostic tests using monoclonal antibodies. Similarly, Kirin Breweries Co., Ltd. is using experience gained in improving the hops and grains used in its traditional beer products to expand into asexual plant reproduction and genetically modified seeds. Of perhaps more interest, however, are the activities of Japanese corporations outside the traditional scope of biotechnology.

Birth of a Bioindustry

Companies that appear to have no logical interest in biotechnology are devoting research funds to this field in both the United States and Japan.

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According to U.S. analysts, most American firms with significant research programs are funding biotech research. In Japan, however, biotech still has the aura of a competitive panacea, attracting participation from an even broader spectrum of businessmen -- more than 600 firms by some estimates. Total Japanese corporate spending in this field generally still is acknowledged to be less than what American firms allocate, but the research also is said to be more focused and aimed chiefly at commercialization.

"Intelligent" materials is the name of a broad category of both organic and inorganic substances that have been tailored at the molecular level for a specific purpose. Through an understanding of how animal or plant biological systems work and of how proteins and other macromolecules are constructed, engineers in a wide range of fields hope to custom design substances with novel qualities. In this area biotechnology overlaps with research into new materials, another area of great interest to Japan. The best-known application of intelligent materials is biosensors, which use proteins connected to electronic devices to measure or detect organic and inorganic substances with great sensitivity or rapidity. Japanese firms are exploring intelligent membranes, coatings, paints, dyes and adhesives.

Biomimetics are artificial products that mimic the function of an organ, body part or biological material. Although biomimetics are not necessarily produced via biotechnology, biotechnology often plays a major role in developing a thorough understanding of the biological archetype that the biomimetic is to replicate. Artificial skin, artificial blood vessels, synthetic ocular lenses all are under development by Japanese companies and often by companies that have no previous experience in the field. Some textile companies, for example, are working on artificial skin and blood vessels using synthetic fibers as a structural matrix. Some biomimetics rely solely on inorganic substances, ceramic bones and teeth for example, while others strive to integrate organic and inorganic materials, as in artificial ligaments.

Japanese progress in bioelectronics is being described as "groping in the dark." At present, many firms are hoping that government-funded projects explicating how the human brain thinks, stores memories and transfers information eventually will lead to electronic devices based on organic molecules, most likely proteins. Such devices would be "assembled" by enzymes under the guidance of artificial genes and consist of molecule-sized components in a three-dimensional arrangement. Bioelectronics promises not only greater speed and compactness than current inorganic electronics but also the potential to exhibit self-regulating and self-repairing abilities. Such devices may be able to endure harsher environments than current equivalents and be shaped to fit any desired space. Most major Japanese computer companies have allocated some money for bioelectronics research to be able to continue to compete if tomorrow's computers look like blobs of gelatin.

Environmental concerns are generating much broader interest in biotechnology than before. Waste treatment firms were early devotees of biotechnology for obvious reasons. Now, however, packaging companies, paper companies, plastics makers and practically every other user of environmentally questionable materials is looking to biotechnology for answers. Some studying the greenhouse effect feel that the ideal answer to too much methane, carbon dioxide, sulphur dioxide and other gases in the atmosphere may be biological processes that fix the gases in solid form. Biotechnical pollution control devices may be in the offing.

Research on outer space applications of biotechnology were dormant in Japan until recently. Problems with the U.S. space shuttle and Japan's nascent efforts to develop a domestic space launch capability dissuaded Japanese firms from investing in microgravity bioprocessing. Excitement over the U.S. space station and even more ambitious plans for manned facilities on the moon and, later, Mars have attracted a host of Japanese entrants. Japanese construction firms, surprisingly, are leading the charge. As part of their efforts to develop extraterrestial habitats they are investigating closed-cycle atmosphere, food and waste-handling systems in which biotechnology will play a major role. Such research clearly is long-term and highly speculative, an approach encouraged by the government.

Government Support

The private sector's focus on commercial R&D concerns government officials who understand the very close link between basic and applied science in biotechnology. Although small compared to U.S. government support for biological science research, every cabinet-level agency allocated some funds or cooperated in some biotechnology project in FY 1989 (see Table). Some participation clearly is token and biotechnology projects are often subsumed under a general category (particularly in the case of cancer research), making it impossible to determine an exact figure for total spending solely on biotechnology. Nevertheless, the bulk of activity is concentrated in a handful of organizations.

- The Ministry of Agriculture, Forestry and Fisheries budgeted a total of Y3.78 billion ($27 million at Y140=$1.00) in FY 1989 for biotechnology and related research. MAFF projects are quite straightforward, dealing mainly with improving plant and marine resources by developing biotechnology techniques and establishing germ plasm repositories.

- The Ministry of Education plays the key role in basic biotechnology research through its support of the national university system and scientific exchange programs. Since researchers within each university set their own research goals, MOE outlays for biotechnology are difficult to calculate. Its National Gene Laboratory (Y196 million or $1.4 million) and international cooperative recombinant DNA programs (approximately Y20 million or $143,000) are exceptions.

- The Ministry of International Trade and Industry has scattered biotechnology projects throughout its broad research funding. Not only is the application of biotechnology in next-generation industries being explored, but its role in revitalizing "old" industries, such as chemicals and mining, also is receiving attention. All told, MITI budgeted about Y6.4 billion ($45.7 million) for biotechnology programs in FY 1989.

- The Science and Technology Agency's support for biotech is divided into two main areas. Cancer research consumed Y8 billion ($57.2 million) in FY 1989, but this included nonbiotech programs as well. The Human Frontiers Science Program, the other main initiative, draws Y1.5 billion ($10.4 million) from STA, and is conducted in cooperation with MITI (which allocated Y932 million or $6.7 million to the project).

HFSP was proposed in 1987 by then Prime Minister Yasuhiro Nakasone at the Venice summit of industrialized nations. In effect, Tokyo is footing the

Japanese Government Biotechnology Research Budget, FY 1988-FY 1989

(in millions of yen)

Agency/Program	FY 1988	FY 1989
Science and Technology Agency		
Human Frontiers Science Program	Y0	Y1,456
Life sciences		
Human biology, aging, brain functions, etc.	2,057	1,861
Cancer research*	6,253	8,014
Environment Agency		
Effluent processing system	245	177
Water pollution treatment	436	382
Solid waste management	146	132
Pollution spill prevention/cleanup*	269	278
Ministry of Education		
Cancer research*	2,207	2,182
National Gene Laboratory	186	196
International recombinant DNA research*	0	66
Ministry of Health and Welfare		
Cancer research*	1,783	1,805
Solid waste management*	95	61
International cancer research	115	129
Pharmaceutical research*	2,600	2,400
Ministry of Agriculture, Forestry and Fisheries		
Basic biotechnology projects	3,665	3,784
Biological information project	167	477
Biological resources evaluation	435	406
Increasing plant yields	448	458
Bionusery system	39	47
Plant cell recombinant DNA	79	81
Advanced biotechnology projects	100	103
Biotechnology promotion at the local level	256	258
Gene bank project	498	513
Other	1,643	1,441
Food industry biotechnology	610	599
Large, high-pressure processing systems	0	139
Agricultural chemicals	0	52
Bioreactor research	235	92
Food testing and purification	106	103
Other	269	213
Local-level projects	200	212

Agency/Program	FY 1988	FY 1989
Ministry of International Trade and Industry		
Human Science Frontiers Program	0	932
Next generation basic industrial technology	1,185	1,160
Bioreactors	197	0
Cell culture technology	422	360
Recombinant DNA technology	319	306
Biomaterials	247	343
Large-scale industrial technology	2,209	2,802
Marine resources*	20	275
Marine technology (Aqua Renaissance '90)*	2,189	2,527
Industrial biotechnology promotion	253	257
Alternative energy		
Alcohol technology	439	518
Biomass projects	15	0
Other	571	1,008
High efficiency alcohol production	190	190
Special projects*	287	310
Mine effluent treatment	53	52
Surveys	0	430
Sunshine plan, bioenergy project	41	26
Industrial base promotion	149	145
Bioindustry promotion	7	6
Bioprocess promotion	5	5
Bioengineering standards	18	13
Bioengineering data base	28	28
Biotechnology patent center	91	93
Safety programs	165	169
Recombinant DNA programs	4	4
Product safety standards	0	50
Outdoor recombinant DNA experiment guidelines	161	101
Biotechnology safety standards	0	14
International cooperation	311	424
Biochemistry projects	4	19
Eucalyptus project (Indonesia)*	0	15
International projects*	303	401
Ministry of Transportation		
Marine research*	95	149
Ministry of Posts and Telecommunications		
High-speed coding technology based on the functioning of the brain	20	24
Network-human interface research*	0	18
Ministry of Construction		
Waste treatment system*	149	114

*Not solely for biotechnology research

Source: Japan Society for the Promotion of Science, Japan Scientific Monthly

bill for Japanese and foreign researchers to explore fundamental biological functions. The idea was so unprecedented that it not only took the ministries a year to agree on the program's basic outline before Mr. Nakasone could announce it, but it took another two years before the program could be initiated. HFSP will focus on two areas: elucidation of how the human brain functions and analysis of biological functions at the molecular level. Originally seen as costing Y1 trillion ($7.1 billion) and lasting 20 years, HFSP has been scaled back to more manageable dimensions. Its first-year agenda will include about 20 three-year, $500,000 research grants, 100 two-year, $100,000 fellowships, 50 short-term, $10,000 fellowships and 10 $10,000 workshops, for a total of around $20.6 million.

International reaction to the program was one of great skepticism. After Tokyo filled in details about funding, intellectual property rights and who would control the research agenda, however, foreign researchers have signed up. While Tokyo sees HFSP as one way of contributing to the global store of knowledge, some foreign observers still feel it is an effort by Japan to buy its way into biotech using foreign labor. Tokyo's commitment to the program, now headquartered in Strasbourg, France, will be watched carefully in years to come.

One area of intense Japanese interest is marine biotechnology. Faced with declining fish stocks in home waters and bans on fishing in waters controlled by other nations, Japan is turning to biotechnology to sustain this important food source. MAFF is focusing on how biotechnology can improve fish resources: larger fish; fish that produce offspring of only one sex; fish that produce more eggs; fish that are genetically programmed to return to their spawning site when mature.

The Environmental Agency and MITI are developing waste treatment and environmental recycling systems based on biotechnology. MITI also is exploring how biotechnology can help extract and refine organic and inorganic materials from the sea and the seabed. In light of ambitious plans to build floating as well as submarine habitats for its population, Japan can be expected to make significant contributions in the area of marine biotechnology.

The rapidly increasing senior citizen population is also driving Japan's biotechnology programs in new directions. There is great concern about the possible economic and social impact of senility and other age-related syndromes in light of lengthening life expectancies and a shortage of younger workers. Projects aimed at understanding the molecular basis of aging, at how the mind stores memories and transfers information and at how cells repair themselves spring from this demographic trend.

Tokyo also supports biotechnology through a system of quasi-governmental organizations. Being outside the traditional Japanese R&D structure, some of these organizations have been successful in sponsoring innovative basic research.

The mission of the Research and Development Corporation of Japan (JRDC), owned and operated by the Japanese government, is to promote basic research with current scientific and social issues in mind. JRDC was created to take over management of the Exploratory Research for Advanced Technology (ERATO) program set up in FY 1981 under the auspices of the Science and Technology Agency. ERATO's purpose is "to foster the creation of advanced technologies and advancing future interdisciplinary scientific activities while searching for a

better system of basic research." Each ERATO project receives up to Y2 billion ($14.3 million) over a five-year period. Spending decisions are made by the head of each project, normally a well-respected researcher from a private company or a public laboratory. Eighteen ERATO projects were in operation or completed in FY 1989 with another three planned for FY 1990. The projects are roughly divided between the physical and the biological sciences. The latter group could make major contributions to the basic science that underlies biotechnology:

- Mizuno Bioholonics project (1982-1987) sought to understand how biological systems organize and process information through the synergistic activities of many units or holons.

- Hayaishi Bioinformation Transfer project (1983-1988) explored the role of prostaglandins in the central nervous system.

- Horikoshi Superbugs project (1984-1989) focused on finding microorganisms that can survive in extreme environments, determining which gene(s) control this trait and replicating them.

- Inaba Biophoton project (1986-1991) is exploring the light generating or absorbing capabilities of biological compounds.

- Hotani Molecular Dynamic Assembly project (1986-1991) is studying how biological systems use molecules to assemble other molecules.

- Kunitake Molecular Architecture project (1987-1992) is developing self-organizing molecular devices that have unusual capabilities.

- Mizutani Ecochemicals project (1988-1993) is exploring chemicals made by plants that affect other plants or animals in the immediate environment.

- Ikeda Genosphere project (1989-1994) seeks to understand how chromosomes exchange parts with other chromosomes during cell division.

The Institute of Physical and Chemical Research (Rikagaku Kenkyusho or RIKEN) was founded in 1917 with the support of the Imperial Household and private companies to provide an environment conducive to basic research. After undergoing wartime and postwar reorganizations, RIKEN was reborn in 1958, returning to its roots as a nonprofit research institute supported by public and private funds. RIKEN has four divisions -- Physics, Applied Physics and Engineering, Chemistry and Biology -- with 10 laboratories each. The Biology group is exploring the use of photosynthesis as an energy source, photochemical and photochemical/electrical reactions and biological control of insects. RIKEN's Life Science Center in Tsukuba is devoted almost exclusively to devoloping basic biotechnology. RIKEN launched the Frontier Research program in 1986 as an interdisciplinary approach to leading edge science. A major theme is understanding how living organisms maintain and regulate the myriad of processes that are going on within them in response to external and internal changes. This includes the molecular basis for aging and self-regulating mechanisms in plants.

The government also has resorted to the tried-and-true method of forming a research consortium of private companies using public funds, if with some

slight twists. The Ministry of Agriculture, Forestry and Fisheries formed in 1986 the Bio-Oriented Technology Research Advancement Institution (BRAIN). BRAIN's 830 private corporate members can apply for low-interest government research loans for agricultural biotechnology research. The Ministry of Health and Welfare formed a similar organization the following year devoted to exploring the secondary effects of drugs and the aging process. While these efforts sound impressive, in fact many of the members joined for strictly financial reasons. Other companies participate in some parts of the research but not others. These groups have run into the usual problems: companies do not assign their best researchers to the project; firms stay away from areas where they have a lead over competitors; the government loans must often be repaid before the research generates profits; and there are disputes over intellectual property rights.

In a slight variation, MITI established the Key Technology Center in 1985 to act as a source of venture capital for innovative research. Among Key-Tech's investments are the Protein Engineering Research Institute and P.C.C. Technology. The former is a group of 14 companies, led by Mitsubishi Chemical Industries, Ltd. and Toray Industries Inc., focusing on industrial applications of engineered proteins. P.C.C. Technology, formed by Mitsui Toatsu Chemicals Inc., Kirin Brewery Co., Ltd., Kyowa Hakko Kogyo Co., Ltd. and four other companies, hopes to develop biotech mass production methods for dyes, perfumes and reagents based on plant-cell engineering.

Obstacles Ahead

Japan's biotech industry has yet to be plagued with the kind of fractious debates over nontechnical issues that have troubled American and European biotech industries. In part this is because Japan simply has followed the lead of the United States in adopting guidelines and safety requirements for biotech experiments and testing, certification, manufacturing and use of biotech products. Japanese society also lacks the tradition of open adversarial debate that has characterized the American approach to these issues. The public has left such decisions to scientists and bureaucrats, who, they feel, have the requisite knowledge to make the best choice. Growing public awareness of global environmental problems and a commitment to play a more active and responsible role in solving such issues as Third World development and North-South relations may spell an end to this quiet approach.

Regulatory/ethical issues - As biotechnology's scope expands and more products come to market, regulatory and ethical issues will become increasingly important. Perhaps the starkest example of the impact that regulations and social ethics can have on the biotechnology industry is the West German situation. Vehement opposition from proenvironment political parties and persistent memories of Hitler's "eugenics" program have combined to make Bonn's regulation of commercial biotechnology applications the strictest in the world. While research is relatively unrestrained, the introduction of genetically altered organisms into an open environment or the use of such microbes for commercial purposes triggers a daunting series of reviews, hearings and permit applications. It has reached the point where most West German firms pursuing biotechnology research have established major research centers outside the country, particularly in the United States. Foreign biotech firms interested in the European market do not consider West Germany a viable site for investment, instead choosing more friendly locations in Great Britain and the Netherlands.

While no one expects Tokyo to ever implement such harsh regulations, tensions are growing between an industry interested in quick commercialization of a wide range of products and a bureaucracy concerned with public safety. The Ministry of Health and Welfare, for example, maintains various approval procedures for items produced by recombinant DNA (rDNA) techniques and traditional chemical methods even when the final product is identical. Since the approval process for rDNA products is longer and more stringent, Japanese biotech companies complain that they are at a competitive disadvantage to those firms using traditional production methods. In addition, Tokyo continues to maintain a strict ban on the release of genetically altered organisms into the open environment, a situation more severe than a restrictive, but adaptable, U.S. attitude. Japanese firms simply have put all such experiments on hold until the government changes its attitude. As there are no signs that a change is in the works at this time, Japanese firms are resigned to moving the tests overseas or abandoning this field to the Americans.

Despite the degree of regulation, there has been almost no public debate over the ethical issues that underpin the government's stance. The rules allow no differentiation between technology that allows early detection of genetic diseases and that which allows employers and insurers to discriminate against those with genetic predispositions for certain ailments. As an example of the power of social mores to hinder technological development, a social taboo on life-sustaining organ transplants has restricted Japan's contribution in this promising medical field. Although this social aversion may be slowly eroding, Japanese researchers and companies continue to place a low priority on this technology.

The most extreme case of using biotechnology for genetic engineering -- that is, arranging for desirable traits in one's offspring -- is a definite possibility and poses extremely sensitive issues. The Japanese public's reticence to debate these options may not serve the country well in dealing with these issues, for if the government takes the easy way out and adopts foreign regulations that prove ill-suited to the Japanese situation, the biotechnology industry could suffer a major setback from a public backlash. At present there are the faintest signs that debate over such issues is beginning in Japan, but there is no way to predict their outcome.

Intellectual property issues - Equally problematic are intellectual property issues. As far as the patenting of genetically altered microbes, other products and biotech processes, Tokyo seems content to follow the lead of the United States, a tack that has drawn little public dissent. The U.S. model, however, may not be the best. American firms complain that the U.S. Patent and Trademark Office takes too long to process an application for biotech products. The PTO reportedly has accumulated a backlog of thousands of biotech applications while issuing decisions on less than a thousand a year. Furthermore, a patent in hand is no guarantee of a commercial monopoly because there are very few precedents to guide judges in biotech infringement cases. For example, a long-running battle between Amgen Inc. and Genetics Institute Inc. over an antianemia drug, erythropoietin (EPO), has taken surprising turns in recent months. In December a judge ruled that both companies were infringing on each other's EPO patents but that Chugai Pharmaceutical Co., Ltd., which had licensed the disputed technology from Genetics Institute and had U.S. marketing rights, was not infringing on Amgen's patents. Since many biotech products are exact or nearly identical copies of naturally occurring substances and since

there is often more than one way to synthesize the substance, conflicts over process patents are inevitable.

Equally vexing is the growing debate over whether nations or individuals have ownership rights with regard to naturally occurring plants, animals or microbes. Biotech companies based in advanced industrial countries scour the globe looking for plants, animals and microorganisms with unique and desirable properties. Seeds of wild plants gathered in foreign countries provide the raw materials for advances in plant breeding; soil samples from around the world may contain the next powerful antibiotic; and cells removed from hospital patients can be grown outside the body and turned into a valuable commodity. There is a heated international debate over whether providers of basic biological material have the right to demand a share of any profits from products developed from that material.

Tokyo has yet to take a definitive position on this issue, but may find itself on the spot, particularly as it tries to respond to international pressures to play a larger role in world affairs and accept greater responsibilities. One area in which Tokyo hopes to showcase its new global status is Third World development and North-South relations. The debate over germ plasm ownership rights is an ideal opportunity for Tokyo to prove its mettle. There is as yet, however, no sign that Tokyo is willing to stake out an independent and perhaps controversial position.

Overseas Moves

Overseas ties continue to form an important part of Japanese biotech companies' strategy. Because cooperation between Japanese university researchers and private firms still is difficult to arrange, interest in tie-ups with foreign researchers remains strong. The United States is still viewed as being on the cutting edge of biotechnology research in most areas, attracting both Japanese and European research funds. Japanese companies are financing work at several U.S. institutions of higher learning, often in exchange for rights to commercialize any advances (see appendix). Newcomers to the prescription drug market, especially firms trying to diversify into new fields, are seeking to quickly build a niche by exchanging money for know-how.

Equally important are ties between Japanese and foreign firms, particularly in the pharmaceutical industry. While many of these links involve technology licensing, also common are distribution agreements and ventures aimed at shepherding new drugs through lengthy government approval procedures. Japanese drug companies understand that the global market will be increasingly treacherous and are trying to establish footholds in overseas markets to weather the assault of larger American and European drug companies.

U.S.-Japan Issues

Although the Europeans have several strong pharmaceutical companies involved in biotechnology, there is general international agreement that the United States and Japan will be the principal competitors. This situation poses the recurring conundrum that has pressured the alliance numerous times before: how to ensure that healthy competition in this commercial field does not threaten friendly overall relations. There is an unfortunate tendency in both countries to characterize the other as posing a life-or-death challenge in biotechnology. Both sides cite the "massive" spending going on in each country as

the reason why still more must be spent or special steps taken at home. There are four particularly thorny issues:

Direct investment - A general perception by Americans -- that their firms are easy to acquire but that firms in Japan are not -- raises significant implications in the biotechnology arena. "Rich" Japanese drug, chemical and other companies are accused of gobbling up small, American biotech startups, draining them of their technology and then using that know-how to strengthen their own competitive position. Or Japanese competitors instantly can win a share of the U.S. market by purchasing an established American distributor or producer. U.S. firms complain that similar opportunities do not exist in Japan, although Merck & Co. sucessfully integrated Banyu Pharmaceutical Co., Ltd. into its operations in 1983.

Reciprocal opportunities would be difficult to achieve for two reasons. First, Japan's biotech industry is populated not by small startups but by medium and large established firms, which are not easily acquired. Second, despite figures showing that mergers and acquisitions in Japan are on the rise (see JEI Report No. 4B, January 26, 1990), traditional Japanese stockholding practices make such transactions difficult even for the Japanese. These two structural phenomena would be difficult, if not impossible, to change via negotiations.

Furthermore, American fears that foreigners are buying up the U.S. biotech industry ignore two things. Many small U.S. biotech startups would fold without cash. In the savings-poor U.S. economy, small firms often find it difficult to raise money. American biotech startups are striking more sophisticated deals with foreign partners, ensuring themselves of exclusive geographic marketing rights or insisting on provisions that prevent the foreign investor from becoming a direct competitor. Large American companies also are actively funding small startups in exchange for technology. Large companies cannot pursue all avenues of research, while small firms cannot afford to invest in full-scale production facilities. By working together, however, they can compensate for each other's weakness.

Technology transfer - Closely tied to the debate over whether the flow of foreign direct investment between the United States and Japan is unequal is the argument over whether the flow of technology is similarly unbalanced. In addition to concern that small American startups are selling their technology too easily or cheaply, some worry that Japanese competitors reap great windfalls from easy access to the U.S. university research system. Free access to the huge volume of basic research performed by American universities may compensate for Japan's acknowledged weakness in this area. Foreign access to Japan's university system is comparable in neither scope nor worth from the American standpoint. Because much of the cutting edge research in Japan is done by private firms, American researchers (academic or private) have little access to what Japan has to offer. Although the Japanese government and companies are expanding their programs for foreign researchers, the flow of information on biotechnology will remain in Japan's favor for some time, providing fuel for American technonationalists.

Patent issues - American displeasure with the Japanese patent system extends beyond the narrow field of biotechnology. Washington is unhappy with both the time it takes the Japanese patent office to process a patent application (an average of more than eight years) and with the quality of protection

granted (for a full discussion see JEI Report No. 8A, February 24, 1989). Washington is not without sin in this area, however. While the overall average pendency period for a U.S. patent application is just 18 months, biotechnology patent applications reportedly require from two-and-a-half to four years to process. The Patent and Trademark Office has promised to speed the process by 1994, but this may be too late for many small American biotech firms. Current negotiations through the Uruguay Round of multilateral trade talks may yield a satisfactory global resolution to these issues. If not, then Congress or the U.S. court system will step in, a potentially less desirable situation for both American and foreign biotechnology concerns.

Cooperative research - Basic research is growing increasingly expensive as scientists pursue understanding at molecular and atomic levels. Since 1985 a semiprivate organization has been trying to launch an international program to determine the code of all human genes. The human cell has 23 pairs of chromosomes and each chromosome is composed of genes linked end-to-end as a strand of DNA. Each gene, in turn, is made up of a very specific (and often long) sequence of just four amino acids. All told, an estimated 3 billion amino acids joined in a very specific order is what defines humans and their unique characteristics. The Human Genome Initiative will take an estimated 15 years and $3 billion to fully decode every human gene. Project leader James Watson (who, with Francis Crick, first explained the structure of DNA) has raised $50 million from the Department of Energy and the National Institutes of Health and has attracted participation from laboratories around the world -- from everywhere except Japan, and that is where the problem lies.

Mr. Watson's plea for at least $300,000 a year from Japan fell on deaf ears, prompting him to threaten to withhold any results from reaching Japan. The problem appears to be that Tokyo has its own human genome project, and it claims that it cannot commit funds to an international project in an era of tight budgets. The Ministries of Health and Welfare and Education are funding genome sequencing efforts in Japanese laboratories to the tune of Y600 million ($4.3 million) and Y250 million ($1.8 million), respectively. STA is encouraging RIKEN to develop automatic gene sequencing equipment with about Y1 billion ($7.1 million) spread over several years. From a foreign standpoint it seems odd that these Japanese efforts, which amount to far more than what Mr. Watson sought, cannot be incorporated or integrated with the Human Genome Initiative, which would be of mutual benefit. Tokyo's stance is even more perplexing given its publicly professed desire to emphasize cooperative R&D and contributions to global science. It is possible that the lack of Japanese participation may become a source of friction, especially if the Human Genome Initiative receives congressional endorsement.

Outlook

Despite the relatively slow pace of commercialization and the potential for friction with the United States, Japanese optimism that biotechnology will sharply improve the globe's standard of living and become a huge commercial market is irrepressible. According to MITI's 1988 biotechnology "vision" or long-term outlook, the Japanese bioindustry in fiscal 1987 was worth Y400 billion ($2.9 billion), of which Y6.5 billion ($46.4 million) was derived from applications of biotechnology. The bioindustry market will grow to Y15 trillion ($107.1 billion) by the turn of this century with biotechnology accounting for Y4.6 trillion ($32.9 billion), MITI forecasts. Even if these estimates prove

wildly optimistic, growth of the Japanese bioindustry probably will outpace every other sector.

According to private sector surveys by the Science and Technology Agency, Japan has set itself high goals. STA's annual white papers reveal a consistent opinion among Japanese scientists and businessmen that while Japan and the United States are about equal in terms of personnel and equipment devoted to biotechnology, the quality of U.S. basic research and the American potential for product development are both far ahead of Japan. (Interestingly, the same surveys show little Japanese regard for European biotechnology efforts.) It is therefore understandable that government programs focus on promoting basic research and the rapid introduction of biotechnology throughout Japanese industry.

Japan's biotechnology industry will continue to internationalize as foreign firms set up research centers in Japan and Japanese firms seek to build positions in markets around the globe. The thorny issues of freedom of foreign direct investment and balanced technology flows pose serious obstacles to the smooth development of Japan's bioindustry. Because these issues affect many industries besides biotechnology, solutions become both more important and more difficult. Questions about the longevity of the Liberal Democratic Party's dominance of Japanese politics plus the lack of a domestic consensus on many biotechnology issues makes quick resolution of frictions unlikely.

Given the enthusiasm of both the government and the private sector toward biotechnology, however, Japan surely will make major contributions to the field in research and commercialization. Whether Japan will make equally important contributions in the areas of bioethics and intellectual property rights is less certain but no less critical to its bid to be a major player in global biotechnology.

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The views expressed in this report are those of the author and do not necessarily represent those of the Japan Economic Institute.

Appendix: Transpacific Activities of Japanese and American Biotechnology Companies

Ajinomoto Co., Inc. - Wister Institute. Research project on a new cancer therapy. (01/87)

Life Technologies Inc. - Oriental Yeast Co., Ltd. Joint venture (Gibco Oriental K.K.) to market a new cell culture in Japan. (01/87)

Dainippon Pharmaceutical Co., Ltd. - Genentech Inc. U.S. firm licensed to produce and market Dainippon's tumor necrosis factor in all countries except Japan, South Korea and Taiwan. (02/87)

Yamanouchi Pharmaceutical Co., Ltd. - T Cell Sciences Inc. Three-year product development agreement for autoimmune diseases and cancer diagnostic products. U.S. firm provides proprietary technology and retains all rights except marketing rights to the new products in Japan, which Yamanouchi will have. (03/87)

Toyo Soda Mfg. Co., Ltd. - U.S. biotechnology research office planned to gather information on genetic engineering, cell fusion and recombinant gene technologies. (03/87)

Upjohn Pharmaceuticals Ltd. - R&D facility in Japan (completed in the fall). (03/87)

Nippon Steel Corp. - Calgene Inc. The Japanese firm will fund Calgene's development of vegetable oil for industrial use in exchange for exclusive marketing rights in the Pacific. (05/87)

Centocor Inc. - Ajinomoto Co., Inc. Marketing tie-up in Japan for U.S. firm's pancreatic cancer drug therapy. (05/87)

Toyo Kasei Kogyo Co., Ltd. - R&D center in Portland, Oregon for manufacturing drug intermediates and raw materials. (06/87)

Toray Industries Inc. - Arthur D. Little Inc. Tie-up to assist Japanese firms in filing life-science registration and product-safety test with U.S. government agencies. (06/87)

Zymogenetics Inc. - Teijin Ltd. U.S. firm licensed its technology for genetically engineered protein C., an anticoagulant. (07/87)

Phillips Petroleum Co. - Kyowa Hakko Kogyo Co., Ltd. U.S. firm to use its recombinant DNA technology to produce salmon growth hormone for Japanese company. (07/87)

Genetics Institute - Neorx Corp. Pooling their efforts to offer their cancer drugs in Japan.

Mochida Pharmaceutical Co., Ltd. - National Cancer Institute. Japanese firm to supply a new beta-type interferon. (08/87)

Murex Corp. - Kyowa Medex Co., Ltd. Joint development of a new line of rapid monoclonal antibody-based assays to screen and diagnose AIDS. Production to be in the United States. (08/87)

Genentech Inc. - Mitsubishi Chemical Industries Ltd. Joint biotechnology marketing agreement. Possible joint research. (08/87)

Applied Biotechnology Inc. - Mitsubishi Corp. Marketing agreement for U.S. firm's live virus vaccine in Japan. (08/87)

Summa Medical Corp. - Cosmo Medical Co., Ltd. Marketing agreement for U.S. firm's monoclonal antibody vaccine in Japan. (08/87)

The Michigan Biotechnology Institute - Marubeni Corp. Marketing agreement for biotechnology products and processes. (08/87)

Teijin Ltd. - Bio-Science Enterprises Inc. Japanese firm acquires American half of joint venture Teijin Bio-Science Laboratories Inc. formed in 1977. (09/87)

Pragma-Biotech Inc. - Eiken Chemical Co., Ltd. After reviewing the U.S. firm's proprietary information on cancer-related biochemical and immunological

methods, Japanese firm to decide whether it will underwrite a portion of the U.S. firm's R&D. (10/87)

Taisho Pharmaceutical Co., Ltd. - Liposome Co. Japanese firm licenses North and Central American marketing rights to its liposomal cardiovascular drug. (01/88)

Suntory Ltd. - Smithkline Beckman Corp. Joint pharmaceutical research and development. (01/88)

Charles River Biotechnical Services Inc. - Its Japanese subsidiary to import Opticell animal cell culture equipment and handle production of monoclonal antibodies for biotechnology firms. (01/88)

Nitto Boseki Co., Ltd. - Subsidiary in Iowa to produced antisera for diagnostic drugs as well as engage in biotechnology research with the University of Iowa. International Immunology Corp. of California, another Nitto subsidiary, will market products. (02/88)

Smithkline Beckman Corp. - Fujisawa Pharmaceutical Co., Ltd. To exchange ownership of their two equally owned joint ventures, leaving the U.S. firm with Smithkline Fujisawa K.K. in Tokyo and the Japanese firm with Fujisawa Smithkline Corp. of Philadelphia. (02/88)

Takeda Chemical Industries, Ltd. - Abbott Laboratories. Joint R&D in America and a manufacturing joint venture in North Chicago since 1977. (03/88)

Hitachi Chemical Co., Ltd. - Biotechnology research center at the University of California, Irvine. (04/88)

Chugai Pharmaceutical Co., Ltd. - Gen-probe Inc. Japanese funding for development of eight viral and two cancer diagnostic products in exchange for exclusive rights to distribute the products in Japan and other selected Asian countries. Gen-probe retains marketing rights elsewhere, subject to payment of a royalty to Chugai for products developed with its funding. (05/88)

Green Cross Corp. - International Genetic Engineering Inc. Joint development of monoclonal drugs for cancer. (05/88)

Olympus Optical Co., Ltd. - Biotechnology laboratory set up in New York City suburb. (05/88)

Eisai Co., Ltd. - Laboratory in Andover, Massachussetts for basic research on antibiotics and drugs to combat senile dementia. (06/88)

Tanabe Seiyaku Co., Ltd. - Immunetech Pharmaceuticals Corp. Limited acquisition (9.5 percent) gives Tanabe exclusive Asian marketing rights to all Immunetech compounds. (06/88)

Fujirebio Inc. - Subsidiary in New Jersey to oversee new drug applications and marketing.

United Biomedical Inc. - Olympus Optical Co., Ltd. Joint development of reagents and marketing agreement in Japan. (06/88)

Chugai Pharmaceutical Co., Ltd. - Upjohn Co. Joint venture to develop and market Chugai's pharmaceutical products in North America. (07/88)

Ajinomoto Co., Inc. - Bristol-Myers Co. Japanese firm to provide two AIDS drugs, DDA and DDI. (08/88)

Nissin Food Products Co., Ltd. - Its Nissin Molecular Biology Institute formed to develop AIDS drugs. (08/88)

California Biotechnology Inc. - Daiichi Seiyaku Co., Ltd. Japanese firm's financing allows it to share U.S. and Canadian marketing rights on an amyloid protein linked to Alzheimer's disease and gives it exclusive rights for the rest of the world. (08/88)

Native Plants Inc. - Kyowa Hakko Kogyo Co., Ltd. - Sumitomo Corp. Joint venture for research in Japan on improved grain varieties through biotechnology. (08/88)

Otsuka Pharmaceutical Co. Ltd. - Micro Vesicular Systems Inc. (an ICI Inc. subsidiary). Joint product development of liposomally encapsulated drugs to treat eye diseases. (09/88)

Bristol-Myers Co. - Sumitomo Metal Industries, Ltd. Joint venture in Japan for conducting immunity tests and other diagnostic procedures and developing diagnostic drugs and medical equipment. (09/88)

Genetic Designs Inc. - Kurabo Industries, Ltd. Agreement for Japanese firm to market U.S. company's synthetic DNA materials. (09/88)

Eli Lily & Co. - A 1983 joint venture between its Hybritech, Inc. subsidiary and Tosoh Corp. dissolved. Tosoh bought its former partner's reagent technology. (09/88)

Chugai Pharmaceutical Co., Ltd. - Upjohn Co. Jointly seeking U.S. government approval for an anemia treatment licensed to Chugai by Genetics Institute, Inc. (10/88)

Kyowa Hakko Kogyo Co., Ltd. - Integrated Genetics Inc. Jointly developing a blood protein essential to regulating platelet production. (10/88)

Itoham Foods Inc. - Biotechnology subsidiary formed in California to produce and market synthesized peptides for medical reagent uses. (10/88)

Eisai Co., Ltd. - Subsidiary set up in New Jersey for clinical testing of antibiotics and drugs. (10/88)

Epitope Inc. - Sakata Seed Corp. One-year pact to explore the use of a gene isolated by Epitope that appears to control a hormone that produces ethylene. (10/88)

Southern Research Institute - Nissho-Iwai Corp. The Japanese firm to seek clients interested in consigning to the Alabama firm their biotechnology experiments. (10/88)

Calpis Food Industry Co., Ltd. - Genentech Inc. Japanese firm licensed its technology for producing the RGF hormone in the development of kidney disease treatments. (12/88)

Kirin Brewery Co., Ltd. - Its biotech research subsidiary will contribute $4 million annually to the La Jolla Institute for Allergy and Immunology. (12/88)

Bio-Technology General Corp. - JCR Pharmaceuticals Co., Ltd. U.S. firm licensed JCR to exclusive Japanese distribution rights for its human growth hormone. (12/88)

Genentech, Inc. - Cancer Center Research Laboratory. Joint research on a gene that inhibits the growth of monocytic leukemia cells in mice. (12/88)

Mitsubishi Kasei Corp. - Kyowa Hakko Kogyo Co., Ltd. - Genentech Inc. Japanese firms helping to get license for blood-clot dissolving agent produced by Genentech. (12/88)

E.I. Dupont De Nemours & Co. - Biotech Research Laboratories Inc. - Sanko Junyaku Co., Ltd. U.S. firms jointly developed AIDS diagnostic kit in Japan. (12/88)

Clonetics Corp. - Kurabo Industries Ltd. Jointly developed a kit to test toxicity of new drugs and cosmetics on human skin. (12/88)

Agri-Diagnostics Associates - Toyo Green Co., Ltd., a subsidiary of Toyo Menka Kaisha Ltd. Japanese firm gets exclusive distribution rights in Japan for U.S.-produced turf disease detection kits. (12/88)

Sumitomo Chemical Co., Ltd. - Regeneron Pharmaceuticals Inc. Japanese firm backs nervous system disorder research in exchange for Japanese marketing rights. (01/89)

Genetics Institute Inc. - Suntory Ltd. Japanese firm buys marketing rights for clot-dissolving agent in Japan, South Korea and Taiwan. (01/89)

Vigilant Products, Co., Inc. - Shikoku Chemicals Corp. Japanese firm to market U.S.-made wastewater treatment enzymes. (01/89)

Mitsubishi Kasei Corp. - Genentech Inc. U.S. firm to conduct clinical trials of Japanese company's blood-clot dissolving agent. (02/89)

California Biotechnology Co. - Kaken Pharmaceutical Co., Ltd. Japanese firm to help with clinical tests of basic fibroblast growth factor. (02/89)

Hitachi Chemical Co., Ltd. - Mast Immunosystems Inc. Japanese firm consigns testing of diagnostic agents to U.S. company. (03/89)

Japan Tobacco Inc. - Mycogen Corp. Joint venture to develop herbicides using microorganisms. (04/89)

Mitsubishi Corp. - Battelle Memorial Institute - Nova Pharmaceutical Corp. Japanese firm to finance research in the United States. (04/89)

Takara Shuzo Co., Ltd. - U.S. subsidiary of Japanese brewer to sell biotechnology products. (05/89)

Schering-Plough Corp.- Kyoto University of Medicine. Cooperative research on leukopenia treatment. (05/89)

Yamasu Shoyu Co., Ltd. - Squibb Corp. U.S. firm gains foreign marketing rights to anti-herpes medication. (06/89)

SS Pharmaceutical Co., Ltd. - Baker Cummins Pharmaceutical Inc. Joint development of AIDS vaccine. (06/89)

Abbott Laboratories - Toyo Menka Kaisha, Ltd. Japanese firm to market biotic pesticide in Japan. (07/89)

United Biomedical Inc. - Olympus Optical Co., Ltd. Japanese firm gains exclusive global marketing rights to AIDS test. (07/89)

Morinaga & Co., Ltd. - Sumitomo Corp. Japanese firms to test microbial pesticide in the United States. (08/89)

Marubeni Corp. - Harris Laboratories Inc. American firm will handle clinical experiments for Japanese firm's clients. (08/89)

Fujisawa Pharmaceutical Co., Ltd. - Lyphomed Inc. Japanese firm acquires Rosemont, Illinois generic drug maker. (09/89)

Shiseido Co., Ltd. - Massachusetts General Hospital. Japanese firm establishes Cutaneous Biology Research Center. (09/89)

NKK Corp. - Battelle Memorial Institute. Joint research on vaccines against respiratory viruses. (10/89)

Yamanouchi Pharmaceutical Co., Ltd. - Beecham Group Plc - T Cell Sciences Inc. Japanese and British firms commission arteriosclerosis research. (10/89)

Biotechnology General Corp. - Nippon Chemical Research Co., Ltd. Japanese company to market American firm's hyaluronic acid developed through bacteria cultures for treatment of arthritis and cataracts. (10/89)

Kyowa Hakko Kogyo Co., Ltd. - Nutri-Quest Inc. American company to develop feeds, feed additives and pesticides with amino acids, enzymes and biotechnology of U.S. research arm of Japanese firm. (11/89)

Kurabo Industries, Ltd. - Clonetics Corp. Japanese spinning firm to market U.S.-developed bioassay toxicity kits. (11/89)

Chugai Pharmaceutical Co., Ltd. - Gen-Probe, Inc. Japanese firm purchases U.S. maker of DNA-based diagnostics. (12/89)

Gene Track Systems Inc. - Nissui Pharmaceutical Co., Ltd. Japanese firm wins exclusive marketing rights at home for DNA- and RNA-based diagnostics. (12/89)

Fujisawa Pharmaceutical Co., Ltd. - University of Pittsburgh. Joint clinical testing of Japanese firm's immunosuppressant. (01/90)

Chromatochem Inc. - NGK Insulators, Ltd. Japanese firm gets exclusive sales rights in Japan for antibody-antigen silica packing agent for affinity chromatography. Also joint development of advanced materials for ion-exchange and gas chromatography. (01/90)

Source: Japan-U.S. Business Report